CASE REPORT

Why are children still being infected with HIV? Experiences in the prevention of mother-to-child transmission of HIV in south London

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Objectives: To evaluate the effectiveness of interventions to prevent mother-to-child transmission of HIV at a large teaching hospital in South East London, and to assess reasons for the small numbers of transmissions that continue to occur.

Design: A database of all pregnant women diagnosed as HIV positive between 1993 and 2005 was reviewed, with detailed (retrospective) case-note review of all mother–infant pairs where HIV transmission occurred.

Setting: King's College Hospital, London, UK, a teaching hospital serving an ethnically diverse and socially deprived population.

Results: 296 pregnancies to 274 women were recorded. 9 of 296 (3.0%) women were lost to follow-up before the end of the pregnancy. Of 287 pregnancies followed up until after delivery, 6 (2.1%) resulted in HIV infection in the infant. More recently, between 2000 and 2004, this transmission rate was even lower, at 3 in 231 (1.3%). Each of these six women had complications, including late presentation to services and defaulting follow-up appointments, which were likely to increase the risk of HIV transmission. Four of the six transmissions occurred in utero.

Conclusion: The overall transmission rate of 2% attests to the efforts of the multidisciplinary care team in managing this population which is often hard to reach. Clearly, good systems are needed to trace those women who default. Further data are needed regarding in utero transmissions.

Mother-to-child transmission (MTCT) of HIV can occur in utero, during delivery and post partum through breast feeding. In the absence of antiretroviral treatment (ART), transmission rates vary from 15% to 40%, depending on maternal viral load, duration of ruptured membranes, the presence of sexually transmitted infections, mode of delivery, prematurity and breast feeding.[1 2]

The highest risk for MTCT is thought to be at the time of labour and delivery.[1] Most HIV infections in infants can be prevented by the timely administration of ART, by caesarean section that is prelabour and prerupture of membranes, and by formula feeding. However, even when all these interventions are successfully implemented, infants may still become infected.

In 2004, 130 children infected through MTCT were diagnosed in the UK. However, at least 61 (47%) of these probably acquired the infection in Africa.[3]

To our knowledge, no review of the reasons for such infections, possible avoidable factors or missed opportunities, has been performed in the UK.

On the basis of a database review of all HIV-positive pregnant women receiving prenatal care at King's College Hospital, London, UK, between 1993 and 2005, we report on the prevention of MTCT at this institution, combined with detailed case-note reviews of all mother–infant pairs where the infant was HIV infected.

METHODS

Setting

South east London is the part of the UK most affected by HIV.[4] In all, 448 women aged 15–44 years are currently being followed up at the King's College Hospital HIV clinic. Of these, 339 (73.4%) are black African, 70 (15.6%) are black British or Caribbean and 34 (7.6%) are white patients; 15 (3.3%) women belong to other ethnic groups. About 4500 pregnant women deliver at the King's College Hospital annually. In 2003, the prevalence of HIV from anonymous antenatal surveillance was approximately 1.0%.[4] HIV-infected pregnant women are managed according to local and national guidelines.[5]

Data analysis

The PREGNET database was developed at King's College Hospital. It includes all HIV-infected women seen for antenatal care since 1993. The following maternal data are included: age, ethnicity, date and place of HIV diagnosis, CD4 cell count and HIV1 viral load at the first antenatal booking and at the last visit before delivery, details of ART, whether caesarean section was performed and pregnancy outcome. After delivery, the results of all blood tests performed on the infant and the child's eventual HIV status are recorded. Any data missing from PREGNET were supplemented with data from clinical records, if available.

All infected infants were identified from PREGNET. To ensure that no cases were missed, we also inspected records of the local paediatric HIV clinic.

Two paediatricians and an HIV physician experienced in the care of pregnant women reviewed clinical records of infants in parallel with those of their mothers. In each case, they estimated the probable timing of infection, and identified any avoidable factors and missed opportunities.

HIV-infected infants were identified as those aged $\leqslant$18 months who had a positive HIV-specific test—that is, HIV culture, RNA polymerase chain reaction, DNA polymerase chain reaction or p24 antigen—or those $\geqslant$18 months who had a confirmatory HIV-antibody test.

The minimum standard for testing in children was two negative HIV-specific tests after age 1 month or a negative HIV-antibody test after 18 months. As the study was conducted over a long period, the specific test used varied over time.

Abbreviations: ART, antiretroviral treatment; IQR, interquartile range; MTCT, mother-to-child transmission

A positive HIV-specific test within the first week of life was used to distinguish in utero infection from intrapartum transmission.[6–8]

RESULTS

In all, 296 pregnancies to 274 women ended between 1 October 1993 and 1 October 2005. Five pregnancies ended between 1993 and 1996, and the remaining 291 from 1997 onwards. In all, 153 of 274 (55.8%) women were diagnosed during routine antenatal screening, which started on an opt-in basis in 1995 and switched to an opt-out basis in December 1998. The rest were known to have HIV when they conceived.

Of the 296 women, 9 (3.0%) were lost to follow-up before the end of the pregnancy—in at least one case the woman was deported. Thus, 287 were followed until after delivery.

In 17 of 296 (5.7%) pregnancies, the mother did not receive ART—all but one of these women refused ART. One mother refused ART in both her pregnancies. In all, 66 of 296 (22.3%) women received zidovudine monotherapy—51 (17.2%) after 2000. Of the 296 women, 209 (70.6%) received ART consisting of ⩾3 drugs during pregnancy, and 1 (0.3%) received two drugs during pregnancy. In all, 3 of 287 (1.0%) women for whom details about delivery are available received ⩾2 drugs during labour only. In 35 of 296 (11.8%) cases, the mother was already receiving AVT at the start of pregnancy, and this was continued throughout pregnancy, and 174 (58.8%) women started ART during pregnancy.

One woman was infected with HIV2. For women with HIV1, the median CD4 count was 302 (interquartile range (IQR) 189–474) cells/mm^3 at first antenatal visit, with a median viral load of 9000 (IQR 2180–29643) copies/ml. The median CD4 count was 359 (IQR 247–494) cells/mm^3 at last antenatal visit, with a median viral load of 57.5 (IQR 50–316.5) copies/ml. Among women receiving a combination of three-drug ART at this time, the median viral load was 50 (IQR 50–143) copies/ml.

Data on mode of delivery were poorly recorded in both the database and patient notes. For this reason, no accurate data are available on mode of delivery for all the women. For the period of this review, all women were advised to have a caesarean section.

In all, 6 of 287 (2.1%) pregnancies followed until after the delivery resulted in HIV infection in the infant. Among 231 of 287 (80.5%) women receiving specialist HIV antenatal care between 2000 and 2004, the transmission rate was 1.3% (3/231).

Summary of cases

Tables 1 and 2 summarise the clinical and laboratory details of the mothers and infants where MTCT occurred. A history of each case as well as the most recent outcome in the infant are given in chronological order below.

Case 1: 1999

This woman had HIV diagnosed at 14 weeks' gestation during routine antenatal screening. As she did not require ART for her own health, it was planned to start ART in the third trimester. She was known to have cervical incompetence, and had a suture placed at 12 weeks' gestation to prevent premature labour. She was seen again at 22 weeks' gestation, but she opted to defer ART. However, she presented with discharge and herniation of membranes at 23 weeks' gestation. She received antibiotics, but went into labour a few days later. She received intravenous zidovudine and a single dose of nevirapine during an emergency caesarean section performed within 2 hours of rupture of membranes. She delivered a premature infant who immediately required mechanical ventilation.

The infant received zidovudine for 6 weeks and a single dose of nevirapine, and was formula fed. HIV-specific tests were positive at birth. Zidovudine, lamivudine and nevirapine were initiated at 10 months at a CD4 count of 1467 cells/mm^3 and a viral load of 58 260 copies/ml.

Case 2: 1999

This woman presented for care at 38 weeks of pregnancy. She had been diagnosed with HIV just 1 week previously.

She was started on zidovudine, didanosine and nevirapine at 38 weeks and she delivered by elective caesarean section 1 week later.

The infant received one dose of nevirapine and was treated with zidovudine and didanosine for 6 weeks. The infant missed HIV follow-up appointments because of undergoing corrective surgery, and was diagnosed as HIV infected at 10 months. At this stage, there were signs of failure to thrive, hepatosplenomegaly and lymphadenopathy, and treatment with zidovudine, lamivudine and abacavir was started.

Case 3: 2002

This woman was screened for HIV at the antenatal clinic when she presented at 31 weeks' gestation. She failed to attend further antenatal appointments despite efforts to contact her. As a result, she did not receive the positive test result, and subsequently could not be referred to the specialist HIV antenatal clinic. She delivered an infant by normal vaginal delivery at 37 weeks.

She was informed of her HIV diagnosis hours after the delivery, but, by this time, had breast fed her baby for up to 4 hours. The baby immediately received post-exposure prophylaxis with a single dose of nevirapine and was started on zidovudine. The baby was subsequently formula fed. The baby's HIV infection was confirmed at 2 weeks of age, and zidovudine was stopped.

Case 4: 2002

This woman was diagnosed during antenatal screening at 25 weeks' gestation. Zidovudine, didanosine and nevirapine were initiated at 27 weeks' gestation. At 36 weeks' an ultrasound scan showed oligohydramnios.

At 36 weeks, she went into labour and rapidly had an emergency caesarean section before rupture of membranes.

The infant received zidovudine for 4 weeks and was formula fed. HIV-specific tests were positive at birth.

Case 5: 2003

This woman had visited Africa at 22 weeks' gestation and again at 28 weeks'. She was diagnosed with HIV during routine antenatal screening at 30 weeks, and was immediately started on zidovudine, lamivudine and nevirapine.

Days later, she presented with fever and contractions. She was diagnosed with falciparum malaria (8% parasitemia), for which she received intravenous quinine. Her haemoglobin dropped from 11.4 to 7.4 g/dl. She recovered from the malaria, and requested a vaginal delivery as she had previously had multiple normal deliveries and had a viral load of only 542 copies/ml. She had a spontaneous vaginal delivery at 38 weeks' gestation. Postnatally, she was also diagnosed with pulmonary tuberculosis.

The infant was diagnosed with HIV at 2 weeks. The infant was started on lamivudine, abacavir and lopinavir/ritonavir at 10 months as it was failing to thrive and had hepatosplenomegaly.

Case 6: 2004

This woman had a negative HIV test at 13 weeks' gestation. She had an HIV-infected partner. At 32 weeks' gestation, she

Table 1 Characteristics of HIV-infected mothers where vertical transmission occurred

Patient	Year of delivery	Antenatal diagnosis	ARV before pregnancy	ARV during pregnancy*	CD4 cell count (cells/mm^3)†	Plasma HIV1 (copies/ml)†	CD4 cell count (cells/mm)‡	Plasma HIV1 (copies/ml)‡	Caesarean section
1	1999	Yes	No	No	233	23 587	233	23 587	ECS
2	1999	Yes	No	AZT, ddI, NVP (1 week)	204	110	204	55	PLCS
3	2002	Yes	No	No			198	101 663	No
4	2002	Yes	No	AZT, ddI, NVP (9 weeks)	298	27 179	510	412	ECS
5	2003	Yes	No	AZT, ddI, NVP (8 weeks)	88	230 325	159	542	No
6	2004	Yes	No	AZT, 3TC, LOP/R (3 weeks)	869	402 000	735	744	ECS

3TC, lamivudine; ARV, antiretroviral drug; AZT, zidovudine; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; ECS, emergency caesarean section; LOP/R lopinavir/ritonavir; NVP, nevirapine, PLCS, prelabour prerupture of membranes caesarean section.
*ARV drugs before and during pregnancy are given in order of administration, with the duration of each treatment in parentheses.
†Earliest available values during pregnancy.
‡Value closest to the date of delivery.

experienced a flu-like illness. She tested HIV-antibody positive at 34 weeks.

At this stage, she was started on zidovudine, lamivudine and lopinavir/ritonavir. Her adherence to ART seemed to be adequate, and therapeutic drug monitoring confirmed therapeutic lopinavir trough levels.

She failed to attend her antenatal appointment at 37 weeks. A few days later she had spontaneous rupture of membranes, and she delivered by emergency caesarean section within 2 h of rupture of membranes.

The infant received zidovudine and lamivudine for 4 weeks and nevirapine for 2 weeks, and was formula fed. HIV infection was confirmed at age 3 months. At age 4 months, the viral load was 200 000 copies/ml, with a CD4 cell count of 308 cells/mm^3.

DISCUSSION

The rate of MTCT of 6 infections in 287 pregnancies (2%) is comparable to that reported in clinical trials in developed countries where all women received ART and delivered by caesarean section.[9]

In each of the six cases, there were complications that were likely to increase the risk of HIV transmission.

All the six women described here were diagnosed antenatally. However, not all received appropriate treatment—in one case because of unexpected premature delivery, and in another because the woman failed to attend follow-up, resulting in her not being informed of her HIV result. All six children received appropriate ART according to the current standard of care.

All mothers diagnosed antenatally were recommended elective caesarean sections. For the six cases, this was accomplished in only four (67%).

Four of the six children tested positive for HIV by an HIV-specific test (culture, polymerase chain reaction or p24) within the first week of life, suggesting that they were infected in utero.

A low viral load at the time of delivery helps to protect against infant infection. Four of these six women had a viral load of <1000 copies/ml near delivery. However, of the four children, two were found to have been infected in utero. In utero infection at a maternal viral load of <1000 copies/ml has been reported previously, but is rare.[10] Although there is no firm evidence, it may be that a high initial viral load in pregnancy that is not optimally treated may be a predisposing factor for in utero transmission of HIV.

Case 1 represents in utero HIV transmission associated with prematurity. HIV-infected pregnant women who receive inadequate prenatal care or do not participate in prenatal care are more likely to deliver infants who are of low birth weight, premature or small for gestational age.[11] Pre-term delivery is strongly associated with intrapartum transmission, especially if membrane rupture is prolonged.[12] Low birth weight has been associated with both in utero and intrapartum transmission.[13]

One of the few transmission categories not adequately targeted by the current UK guidelines are the early in utero infections. Current guidelines set by the British HIV Association recommend treatment of HIV-infected pregnant women who do not require ART for their own health after the second

Table 2 Characteristics of HIV-infected infants

Patient	Gestational age at delivery (weeks)	Fetal Weight (g)	Antiretroviral drugs received*	HIV1 DNA PCR†	p24 antigen†	Likely timing of transmission
1	24	954	AZT (6 weeks), NVP (1 dose)	Positive (birth)	Positive (birth)	In utero
2	39	2900	AZT, ddI (6 weeks), NVP (1 dose)	Negative (birth), positive (10 months)	Negative (birth) Positive (10 months)	Intrapartum
3	37	2900	AZT (2 weeks), NVP (1 dose)	Positive (birth)	Positive (birth)	In utero
4	36	3500	AZT (4/52)	Positive (birth)		In utero
5	38	2700	AZT (4 weeks)	Equivocal (birth), positive (2 weeks)	Positive (3 months)	In utero
6	37	3080	AZT, 3TC (4 weeks)	Negative (birth), positive (3 months)	Negative (birth and 3 months)	Intrapartum

3TC, lamivudine; ARV, antiretroviral; AZT, zidovudine; d4T, stavudine; ddC, zalcitabine; DDI, didanosine; NVP, nevirapine.
*ARV drugs are given in order of administration, with the duration of each treatment in parentheses.
†Value in parentheses indicates age (weeks) at which test was done.

Key messages

- Low rates of mother-to-child transmission (MTCT) of HIV are seen in this UK cohort, attesting to strong multidisciplinary teams.
- In cases of MTCT, complicating factors are usually present.
- Some MTCT occurs early in utero and starting antiretroviral treatment early should be considered, particularly in women with a history of preterm labour.

trimester.[5] We believe that their future guidelines should specifically consider the issue of earlier initiation of ART in women who have a history of preterm labour.

In case 1 with a known history of preterm labour, early initiation of ART after the first trimester may have prevented MTCT.

Case 3 represents several potential missed opportunities. Despite numerous attempts to contact her, this woman was not informed of her diagnosis until after delivery, and breast fed her infant for several hours. Studies have shown a considerable incremental risk for HIV acquisition in the infant on the basis of duration of breast feeding.[14] Although this could potentially have been an avoidable factor if the infant had been born HIV uninfected, this infant was shown to have been infected in utero. As a result of this case, a system to flag HIV-positive results was introduced at King's College Hospital. Improved communication and flagging of positive results would be an important safeguard to add to any antenatal care programme.

In case 5, other coinfections (in this case malaria and mycobacterium tuberculosis infection) may have enhanced the risk of MTCT by causing a placentitis before ART was initiated.

Dual infections with HIV and malaria during pregnancy have been associated with low birth weight, preterm delivery, intrauterine growth restriction and anaemia,[15] which may all affect the HIV status of the infant. Placental malaria occurs more commonly in HIV-infected women, and those with placental malaria are more likely to transmit HIV to their infants (40% *v* 15.4%).[16] This highlights the importance of discussing any travel plans and malaria prophylaxis (at the outset). Consideration should be given to screening people who have recently travelled to an area of high malaria risk.

Case 6 represents acute HIV seroconversion in pregnancy. Several authors have shown an increased risk for sexual transmission of HIV during seroconversion,[17] and several case reports have documented MTCT in this setting.[18] It is likely that the virus is more efficiently transmissible, either horizontally or vertically, during seroconversion. However, a large Thai study did not find increased transmission rates among women who seroconverted during pregnancy.[19]

Higher rates of disease progression have been reported in infants infected in utero.[8] Despite four of the six children in this series being infected in utero, none has experienced rapid disease progression. At the present time, three are receiving ART.

Although this review identified potential missed opportunities and avoidable factors, no infections could be directly attributed to any of these. In general, the mothers received appropriate prenatal care and advice, and all six infants were appropriately managed after delivery.

The low transmission rate of $\leqslant 2\%$ in the multicultural population served by King's College Hospital attests to the efforts of a multidisciplinary care team dedicated to the care of this population which is often hard to reach. Social disadvantage, poverty, belonging to minority ethnic groups, late antenatal booking, poor antenatal attendance and substance misuse are all known risk factors for poor obstetric outcomes[20]: the avoidable factors for MTCT identified in this study reflect this. Special antenatal outreach services for HIV-infected women in these risk groups, targeted community-based education programmes and systems to trace women testing HIV positive during antenatal screening who default from antenatal follow-up may deal with with some of the avoidable factors identified and may further reduce the risk of vertical transmission of HIV.

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